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Infectious Diseases, the ABO Blood Groups and Human Evolution

SINCE IT IS important to direct in the best possible way the future evolution of man it is obviously useful to understand how human evolution has occurred in the past. Although man does not differ from other living forms in being subject to the interaction of heredity and environment, his long generation time tends to obscure the reality of the processes of selection. In addition many human characteristics such as stature, form and vigour though of great evolutionary significance are influenced by hereditary processes which involve the activity of many genes. Such multifactorial inheritance while it is undoubtedly of great importance is difficult to study; consequently a few "simple" polymorphic systems have received an undue degree of attention. Nevertheless it is in these simple polymorphic systems that a great deal of recent work has confirmed the classical statements Fisher (1930) and Ford (1942). Fisher stressed the rarity of genes of neutral selective value while Ford suggested that the blood groups were balanced polymorphic systems probably associated with resistance to disease. Investigation into the truth of this hypothesis can hardly fail to illuminate to some extent, the process of human evolution by selection.

The ABO Blood Groups

The last few years have seen a tantalizing extension of our knowledge of the evolutionary significance of the human blood groups. Since 1953 several research teams, particularly those led by Aird and by Clarke have firmly established the association of the ABO polymorphism with liability to diseases involving the function of organs derived from the embryonic foregut. Evidence, overwhelming in some cases and strong in others has accumulated for associations between the ABO blood groups and duodenal ulcer, gastric ulcer, gastric carcinoma and pernicious anaemia. These associations and others less certain or certainly negative are reviewed by Clarke (1961).

Potential sources of selection

Since most of the diseases which have been associated with the ABO blood group system exert their morbidity and mortality comparatively late in life, it has been suggested that the principal selecting mechanisms acting on the ABO polymorphism occur in foetal or in neonatal life. The protective effect first suggested by Levine (1943) of ABO incompatibility (between mother and foetus) on babies liable to rhesus erythroblastosis foetalis is just such a mechanism. However, in terms of the major causes of premature death in human populations and therefore of the great potential sources of evolutionary selection, famine and pestilence may be considered pre-eminent even to-day. These factors have been reviewed by Motulsky (1960) and as an example the effects of malaria on human evolution may be quoted. There can be little doubt that malignant tertian malaria is operating at the present time as a selecting agent maintaining at least two genetic traits, sickle cell and glucose 6 phosphate dehydrogenase deficiency, in high frequency in many areas of the world where this form of malaria is common. Other infectious diseases which are or have been associated with

a high mortality, particularly amongst the young and fertile must have been similarly potent factors selecting for survival individuals carrying genes which protected against death from such diseases. For the reasons which were discussed earlier, it was inevitable that the blood groups should be investigated in relation to infectious diseases, and statistically significant associations between the ABO groups and rheumatic heart disease and with virus respiratory disease have been reported.

Rheumatic Heart Disease

Streptococcal throat infections are followed by damage to the heart only in a few cases and the majority of infections are not followed by this complication. Glynn *et al.* (1956) postulated. that host variation was an important factor in determining the occurrence of such rheumatic carditis. Clarke *et al.* (1960) and Buckwalter *et al.* (1962) have been able to demonstrate that amongst these host factors were included the ABO blood groups.

Amongst proven cases of rheumatic heart disease there is a significant reduction in the incidence of individuals of group O. This may be interpreted as an increased liability of patients who are non-O to develop heart disease following infection with streptococci and there is general agreement that as Glynn *et al.* (1956) had suggested this tendency also occurs in individuals who are non-secretors of ABO (H) blood group substances.

Respiratory Viruses

McDonald and Zuckerman (1962) reported the blood group frequencies in a group of 1,685 R.A.F. personnel who had been treated for respiratory illness associated with identified virus infection. In their series there was a highly significant excess of group O patients and a corresponding deficiency of group A in the influenza A_2 infections compared with 47,108 R.A.F. recruits used as controls. A reverse trend but of lesser degree was noted with the adenovirus group. It was concluded that in the conditions prevailing persons of blood group A had been at an advantage. The secretor status of their patients was not quoted.

Methods and Controls

These studies of rheumatic fever and viral respiratory infections are, like the earlier work, dependent on comparing the ABO phenotype frequencies in a disease group with those in controls. Quite complicated statistical manoeuvres are necessary to avoid the gross errors potentially inherent in such a comparison. The most obvious of these is ensuring that the disease and the control groups are derived from the same parent population which itself is of homogeneous blood group proportions. Penrose (1959) pointed out again that patients with some diseases might be of an inbreeding strain with high susceptibility to the disease and with different blood group frequencies from the rest of the population (incomplete miscegenation or stratification). Use of suitable statistical methods (e.g. that of Woolf, 1955) largely avoids this error. However, such methods are not infallible and cannot compensate for bias (Buckwalter *et al.* 1962). Nevertheless the great care which has been associated with much of this work has made it virtually certain that the comparable results which have been obtained from different centres in fact represent a genuine relationship between the blood groups and some diseases.

The meaning of the associations is quite unknown. It is not clear for example whether the physical presence of blood group substance determines differential susceptibility or whether the various phenotypic expressions of the ABO polymorphism are merely indicative of a more profound metabolic variability governing susceptibility to disease. The resolution of this problem is essential to our conception of the rôle played by the blood groups in the heritable component of acquired disease.

Widespread occurrence of ABO (H) substances

In this connection it is interesting to note the widespread occurrence of ABO (H) blood group substances in animals and plants (Mourant 1956) and in micro-organisms in particular (Springer 1961). Since some of these micro-organisms may be pathogenic to man it is inevitable that those interested in evolution will be intrigued by such an occurrence of antigens common both to host and parasite and will speculate upon its significance. It has occasionally been implied that the

coincidence is fortuitous and has no significance. This argument is only likely to influence geneticists convinced of the existence of genes neutral in selective value and several attempts have been made to demonstrate a mechanism by which the occurrence of ABO (H) substances in pathogens could be a factor in the individual variation of human resistance to infection.

Plague and Smallpox

Notable amongst these has been the work of Pettenkofer and his colleagues (1960, 1961, 1962). These workers were convinced that the global variations in frequency of the ABO blood group types (ABO polytypism) could depend on differential response to infection with potentially lethal diseases, especially those that occurred previously in major pandemics of very high mortality. They studied two organisms of potential, and previously actual, pandemic lethality, *Pasturella pestis* and variola—the agents of plague and smallpox respectively. They claimed to have detected material indistinguishable from human blood group H substance in *P. pestis* and A substance in the strain of vaccinia (closely related to variola) which they studied. The methods used included the inoculation of suitable rabbits with material prepared from cultures of the appropriate organisms, *P. pestis* on blood-group-substance-free agar medium and vaccinia on chick chorio-allantois. The serum obtained after inoculation with *P. pestis* material contained antibody which agglutinated human O cells (containing H substance) and was removed (absorbed) by "H" substance and by suspensions of *P. pestis*. Similarly anti-A induced in rabbits inoculated with vaccinia material agglutinated human blood group A cells and was absorbed by A substance and by preparations of vaccinia. It was suggested that Anti-H "reacts" with *P. pestis* and naturally occurring anti-A with variola to produce a result favourable to the host.

The inferences drawn from these findings were that individuals of group O since they possessed the "H" antigen would be unable to develop anti-H in response to infection with the H-containing plague organism and would be more likely to succumb than contacts of other ABO groups. Similarly individuals of groups A and AB lacking anti-A would be more susceptible to the A-containing smallpox virus. Where both diseases were common a relative preponderance of group B individuals would eventually occur. Just such a preponderance, it was pointed out, exists in the uniquely high frequency of blood group B in Asia where both plague and smallpox have caused frequent and severe epidemics.

In support of their hypothesis Pettenkofer and his colleagues claim to have demonstrated that in India and Pakistan individuals of groups O and B infected with smallpox may have a slightly more mild attack than those of group A and AB.

This work of Pettenkofer and his colleagues has been subjected to much criticism. Harris *et al.* (1962), although confirming the ability of vaccinia preparations to induce anti-A antibody formation in rabbits, demonstrated the presence of a similar property in uninfected egg membranes. In addition they were able to show that vaccinia virus grown on rabbit dermis and uncontaminated with chick egg material did not induce anti-A antibody formation, results which appeared to remove the experimental basis for the presence of blood group A substance in vaccinia virus and probably variola. In addition Harris and his colleagues failed to neutralize vaccinia virus with potent rabbit anti-A and a further attempt to substantiate the relationship between vaccinia virus and blood group A substance by growing the virus in the presence of A or B blood group substances also failed. There was no difference between A and B substances in the degree of potentiation which occurred. Since vaccinia virus probably does not contain blood group A substance, is not neutralized by anti-A serum and its growth is not selectivly enhanced by blood group A substance, there is at present no explanation for the results claimed by Pettenkofer and his colleagues (1962), that susceptibility to smallpox and response to vaccination are statistically greater in humans of blood group A and AB than of blood groups B and O. The possibility remains that individuals of different blood groups may have greater or lesser resistance to smallpox not because of any particular attribute of their blood group but because they have been derived from different stock. Thus the

apparent susceptibility of group A and AB individuals may be due to an influx of A genes into India from an area of low smallpox endemicity. If, however, it is firmly established from a number of different centres, that individuals of group A and AB are more susceptible to smallpox (and vaccination) than are O and B then this observation will be analogous to those relating to rheumatic carditis and respiratory virus infections, where the causative organisms have not been shown to contain ABO (H) substances. The presence of H substance in the epidemic strains of plague bacilli has been questioned by Springer and Wiener (1962) and since most individuals irrespective of group are likely to have some H-antigen these authors were unconvinced that group O individuals were less likely to develop anti-H following infection with plague.

Prospects

Thus the attractively simple immunological relationship involving human blood group antibodies and micro-organisms containing blood group antigens has not been either proved or disproved, although the weight of evidence seems against it in smallpox and plague. On the other hand Muschel and Osawa (1959) have shown that anti-B sera exerts a bactericidal effect against *Escherichia coli* 086, a bacillus containing high group B activity. They conclude ". . . Cross-reactivity between blood group substance B and *E. coli* 086 affords a model for the possible influence of blood groups in resistance to infection against those microbial agents which may possess blood group antigens."

There is little doubt that the controversial nature of this subject will provoke many future "alarums and excursions". It is therefore important to remember that the study of the blood group systems in relation to diseases, infectious and non-infectious, is merely an imperfect tool with which we may hope to gain some insight into the processes of human development and evolution.

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